# Characterization of Liver Pathogenesis and Human Immune Responses in a Humanized Mouse Model of Hepatitis C Virus Infection

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**Background/Objective**

Hepatitis C virus (HCV) infection affects millions of people worldwide and many patients develop chronic infection leading to liver cancers. For decades, the lack of a small animal model that can recapitulate hepatitis C virus infection, its immunopathogenesis and disease progression has impeded the development of an effective vaccine and therapeutics. We aim to provide a humanized mouse model for the understanding of HCV-specific human immune responses and HCV-associated disease pathologies.

**Method**

Recently, we have established human liver cells with a matched human immune system in NOD-scid Il2rg-/- (NSG) mice (HIL mice). These mice were infected with laboratory and clinical isolates of HCV by intravenous injection. Viral replication and pathogenesis were investigated by using a comprehensive panel of assays including reverse-transcription real-time PCR, cytokine profiling and immunohistochemistry.

**Result**

In this study, we demonstrate that HIL mouse is capable of supporting HCV infection as evident from the expression of viral proteins in the in situ reconstituted human hepatocytes. Productive replication resulted in increasing levels of intracellular viral RNA from 2 weeks to 5 weeks post-infection and the appearance of double-stranded RNA. Interestingly, the infected mice also presented some of the clinical symptoms found in HCV-infected patients including hepatitis, robust virus-specific human immune cell and cytokine responses as well as liver fibrosis and cirrhosis. Similar to results obtained from the analysis of patient samples, the human immune cells, particularly T cells and macrophages, play critical roles during the HCV-associated liver disease development in the HIL mice. Furthermore, our model is demonstrated to be able to reproduce the therapeutic effects of human interferon alpha 2a (IFN $\alpha$ -2a) antiviral treatment.

**Conclusion**

The HIL mouse provides a model for the understanding of HCV-specific human immune responses and HCV-associated disease pathologies. It could also serve as a platform for therapeutic drug testing and vaccine development.